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THE ASSOCIATION BETWEEN CYTOMEGALOVIRUS (CMV) INFECTION, OBESITY AND METABOLIC SYNDROME IN US ADULTS: NHANES 1999-2004

BY

Shannon Fleck
Degree to be awarded: MPH
Executive MPH

William McClellan, MD, MPH Committee Chair	**Date**
Janet Wojcicki, PhD, MPH Field Advisor	**Date**
Kevin Sullivan, PhD, MPH, MHA Associate Director, Applied Epidemiology	**Date**
Melissa Alperin, MPH, MCHES Chair, EMPH Program	**Date**

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BY

Shannon Fleck
MPH, Emory University, 2014
BS, University of California, Davis, 2008

Thesis Committee Chair: William McClellan, MD, MPH

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Abstract

THE ASSOCIATION BETWEEN CYTOMEGALOVIRUS (CMV) INFECTION, OBESITY AND METABOLIC SYNDROME IN US ADULTS: NHANES 1999-2004

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Background: Metabolic syndrome (MetS) is a constellation of risk factors - including increased waist circumference, high blood pressure, hypertriglyceridemia, low HDL-cholesterol and elevated fasting glucose - that usually manifest in the setting of obesity. However, the presence of chronic inflammation is believed to be a distinguishing factor for why some develop MetS, but others do not. The purpose of this analysis was to determine whether a common pathogen, cytomegalovirus (CMV), was associated with an increased prevalence of MetS, and whether this relationship was influenced by obesity.

Methods: Data from the National Health and Nutrition Examination Survey (NHANES) were pooled for the years 1999-2004 for this analysis. The study population was limited to adults between 20-49 years of age who participated in the fasting sub-study (n=2,532). Logistic regression was used to obtain prevalence odds ratios (OR) for assessing the association between CMV and MetS stratified by BMI category (normal weight, overweight, obesity and extreme obesity); Poisson regression was used for examining the association between CMV and count of individual MetS components.

Results: In unadjusted analyses, CMV was significantly associated with MetS in females (OR: 1.50; 95% CI: 1.1-2.1), but not in males (OR: 0.99; 95% CI: 0.9-1.1). After stratifying by BMI and poverty level and adjusting for age, race/ethnicity and smoking status, the odds of MetS was significantly higher in CMV+ normal weight females above or at the federal poverty level (aOR: 43.25; 95% CI: 4.1-452.3), as well as for those below the poverty level (aOR: 146.10; 95% CI: 10.8-1980.3), when both were compared to their CMV- counterparts. Interestingly, in extremely obese females at or above the poverty level, the odds of MetS was 84% lower in CMV+ vs. CMV- individuals (aOR: 0.16; 95% CI: 0.04-0.67).

Conclusions: CMV seropositivity was associated with a higher odds of MetS in normal weight females, but a lower odds of MetS in extremely obese females. These results suggest that the presence of alternative sources of inflammation may be influencing the burden of MetS in adult females.

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INTRODUCTION

INTRODUCTION & HYPOTHESES

Metabolic syndrome (MetS) represents a collection of risk factors that together predispose individuals to type 2 diabetes (T2D) and cardiovascular disease (CVD). At least one quarter of the U.S. population currently meets the criteria for MetS and this high prevalence is considered to be a result of the syndrome's association with the obesity epidemic, of which roughly one third of the population is affected by [1-3]. However, MetS can also present in the non-obese, while at least 30% of the obese population can remain metabolically healthy [4]. Recognition of this "obesity paradox" has helped shift the focus from the presence of obesity per se to the pivotal and deleterious role that chronic inflammation plays in the development of MetS and its components.

In addition to obesity, there are several other causes of chronic and systemic, low-grade inflammation, including long-term exposure to toxins, stress and persistent infections. The purpose of this analysis is to determine whether infection with a common chronic viral pathogen, cytomegalovirus (CMV), is associated with the development of metabolic syndrome. In particular, this relationship will be explored among those with and without overt obesity, in order to examine whether the presence of obesity as an additional source of inflammation magnifies the relationship between CMV infection and MetS.

BACKGROUND & LITERATURE REVIEW

Although precise definitions vary, the components of MetS typically include a measure of obesity, dyslipidemia, elevated blood pressure, insulin resistance, chronic inflammation and a prothrombotic state [5-6]. According to the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III), MetS can be clinically diagnosed when at least three of the following five criteria are met: abdominal obesity, elevated blood pressure, hypertriglyceridemia, low HDL-cholesterol and high fasting glucose [6]. These components are all highly correlated with one another, though obesity is commonly perceived to be the initiator of MetS. Both MetS and obesity can manifest as a state of chronic, low-grade inflammation and altered immune responses [7-8], with obese subjects with MetS exhibiting elevated levels of circulating inflammatory mediators, including the proinflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNFa), as well as the acute-phase reactant, C-reactive protein (CRP) [9]. While obesity is the most noticeable risk factor for MetS, it is actually the inflammation often accompanying obesity that is the pathogenic culprit, rather than simply the over-accumulation of adipose tissue throughout the body. In recent years there has been growing

recognition that chronic inflammation is the true predictor of subsequent metabolic dysregulation [9], with several studies revealing that such inflammation does indeed precede the development of the metabolic disturbances that occur alongside obesity and MetS, as well as T2D and CVD [10-14].

Obesity-induced inflammation results when excess nutrient intake eventually overwhelms the storage capacities of adipocytes, leading to increased levels of circulating glucose and free fatty acids, and oxidative stress. This cellular stress promotes the recruitment of macrophages to adipose tissue and induces the progressive release of proinflammatory cytokines, adipokines and acute phase reactants, creating a positive feedback loop that perpetuates a state of low-grade, chronic inflammation [15]. Adipose tissue from obese individuals contains significantly higher amounts of macrophages and proinflammatory adipokines than adipose tissue from lean individuals [16-17]. Up to 40% of obese adipose tissue can be composed of macrophages, compared to 10% of lean adipose tissue [17]. Alterations in other circulating immune cells have also been reported in the obese [18].

However, inflammation in adipose tissue (and the metabolic dysregulation that results) can still occur in lean, or normal weight, individuals - obesity is not a requirement for developing or diagnosing metabolic syndrome in the U.S. In fact, a portion of the normal weight population exhibits metabolic dysfunctioning, including MetS, while many obese individuals are able to remain metabolically healthy (MHO: metabolically healthy obesity) [19]. This "metabolically obese normal weight" (MONW) phenotype is an insidious yet growing phenomenon. According to Wildman et al.'s analysis of NHANES data from 1999-2004, 24% of the normal weight population was considered metabolically obese, whereas MHO was present in up to 30% of the obese population [4, 20]. Interestingly, MHO is not associated with an increased risk of MetS, T2D, CVD or CVD-related mortality [21], while MONW, particularly in women, can be [20, 22-26]. When compared to their metabolically unhealthy obese (MUO) counterparts, MHO subjects exhibit significantly lower levels of proinflammatory adipokines and appear to be protected from the potentially adverse cardiometabolic effects of their obesity [27-28]. In contrast, MONW subjects tend to have significantly increased blood pressure, levels of triglycerides, free fatty acids and proinflammatory cytokines compared to their healthy normal weight counterparts [29-30], and are at a higher risk for T2D [7, 31]. Together, these data suggest that activation and maintenance of a proinflammatory response is a critical trigger of MetS, as well as an important factor in distinguishing MUO from MHO and MONW from metabolically healthy normal weight individuals.

Consequently, if chronic inflammation is the underlying factor prompting the development of MetS, then alternative sources of chronic inflammation, other than obesity, are likely to contribute to the burden of MetS, as well. The widespread human pathogen cytomegalovirus (CMV) may be one such example. CMV is a beta-herpesvirus estimated to chronically infect over 50% of the population in the

United States [32]. Seroprevalence increases with age, starting at 30-40% within the first year of life [33] and exceeding 90% in those who are 80 years or older [34]. Infection is also more common in females, non-Hispanic African Americans and Mexican Americans [34] and is associated with low household income and education level [32]. CMV can infect a wide range of cell types and tissues and is never truly cleared by the immune system due to several immune evasion strategies employed by the virus [35]. While CMV infection represents a serious threat to fetuses and immunocompromised individuals (such as organ transplant recipients and those infected with HIV), infection in immunocompetent individuals is typically asymptomatic.

Nevertheless, evidence suggests that even in otherwise healthy individuals, latent infection still results in regular subclinical reactivations of the virus, requiring adequate and sustained type 1 T-cell host responses to successfully control and suppress viral replication and dissemination [35-37]. These persistent reactivations throughout the lifetime ultimately lead to 10%-50% of the entire T-cell repertoire being devoted to CMV-specific immune responses [38-39]. Maintaining this constant balance between host and pathogen is likely a significant source of the chronic and low-grade inflammation present in CMV carriers [38, 40-42] and, similar to what is seen in obesity, is accompanied by increased levels of CRP and pro-inflammatory cytokines, including interferon-gamma (IFNg) [43-44] and IL-6 [45-46] in the serum and at the cellular level. Notably, Chan et al. (2008) reported a 280-fold increase in IL-6 and 15-fold increase in TNFa levels in CMV-infected macrophages [41]. It is not surprising, then, that CMV has been implicated in several chronic and inflammatory conditions, including vascular disease [47-48], inflammatory bowel disease [49], immunosenescence [50-51], cognitive impairments [52], some cancers [38, 53], and even overall mortality [54-55], with the list continuing to grow.

Besides CMV's broad pro-inflammatory effects, it is interesting to note that many of the individual components of MetS have also been found to associate with CMV, though the methods and findings of studies investigating this have been sometimes conflicting. For example, in both humans and mice CMV has been found to be an independent predictor of hypertension with infection inducing the release of cytokines known to increase blood pressure [56-57] and CMV IgG antibody titers correlating positively with blood pressure levels [58]. However, a recent analysis of NHANES 1999-2002 data revealed that CMV was no longer a significant predictor of hypertension after age was adjusted for [59], while Vahdat et al. found similar results after adjusting for other potential confounders [60].

The evidence supporting CMV's role in vascular and endothelial dysfunction is more consistent, as it is recognized that CMV readily infects endothelial cells, smooth muscle cells and lymphocytes. Several studies have demonstrated that infection induces the up-regulation of pro-inflammatory

cytokines within the arterial wall, as well as the migration of various immune cells to these sites in the vasculature, resulting in inflammation-induced endothelial cell injury [61-64]. Elevated CMV IgG antibody titers are also correlated with intimal medial thickening [63] and ischemic heart disease [65]. Moreover, circulating CMV particles are able to activate platelets, further promoting immune cell migration and the expression of endothelial cell adhesion molecules [62, 66]. The ongoing pro-inflammatory response to this vascular injury and the prothrombotic state that results are significant contributors to the development of atherosclerotic lesions. The association between CMV and atherogenesis has been investigated extensively, with the majority of studies indicating that CMV either promotes or exacerbates atherosclerosis [33, 48, 63, 67-68], as well as CVD [55, 67, 69-70].

Although far less explored, there also appears to be a connection between CMV and altered lipid and glucose metabolism [71-72]. For instance, serum total cholesterol levels have been found to be significantly higher in CMV seropositive females than in those who are seronegative [73] and serum glucose levels were higher in seropositive elderly individuals, as well as the prevalence of T2D [74]. Cholesterol is a requirement for CMV replication [75] and the virus works synergistically with elevated levels of cholesterol to provoke vascular inflammation [76]. Consistent with these findings, statin therapy has been found to exhibit anti-CMV activity, presumably through its cholesterol lowering effects [77-78].

As evidence continues to emerge supporting CMV's role in exacerbating several of the cardiometabolic parameters that define MetS, it is becoming clearer that the inflammatory milieu of chronic CMV infection resembles what is found in metabolically unhealthy obesity. Based on these prior findings, it is now worth examining whether or not CMV is a predictor of MetS as a whole, in addition to its individual components, and to see if the presence or absence of obesity differentially influences this association.

METHODS

POPULATION

Data from the continuous National Health and Nutrition Examination Survey (NHANES) were pooled for the two-year cycles 1999-2000, 2001-2002 and 2003-2004 for this cross-sectional study. NHANES is conducted by the National Center for Health Statistics (NCHS) and selects a nationally representative sample of the U.S. non-institutionalized civilian population using a complex, multistage probability sampling design. Data was collected at mobile examination centers by in-person interviews, physical examination and laboratory testing of collected blood and urine specimens. Additional

information on how the 1999-2004 NHANES cycles were conducted can be found elsewhere in greater detail [79-80]. This study was exempt from local Emory University Investigational Review Board (IRB) approval.

Individuals who participated in the morning fasting sub-study and had fasted for at least 8 hours were used in this analysis (n=9,529). The sample population was further limited to 2,859 adults who were between 20-49 years of age and had non-missing data for CMV serostatus, Body Mass Index (BMI) and the five components of MetS (based on the NCEP-ATP III guidelines [6]): waist circumference, blood pressure, triglycerides, HDL-cholesterol and fasting glucose levels. Females who had a positive urine pregnancy test or were self-reported as pregnant were excluded from the analysis (n=279), as well as participants with BMI values considered underweight (n=47) or equivocal CMV specific IgG antibody levels (n=1), which yielded a final sample size of 2,532 participants.

DATA COLLECTION & PREPARATION

CMV serostatus was determined by measuring CMV specific IgG antibody levels with an Enzyme Linked Immunosorbent Assay (ELISA) performed by Quest International, Inc. (Miami, FL), The Quest International, Inc. cut-off value of ≥0.80 AU/mL was used to determine seropositivity and values near this cutoff were retested with a second ELISA by bioMerieux (Durham, NC). CMV IgG Optical Density levels were also reported and represent CMV antibody titer, with values greater than the detectable range for the ELISA assigned values of 3.001 AU/mL. Weight and height measurements were collected by trained health technicians and used to calculate BMI (kg/m^2). BMI was divided into four categories: normal weight (18.5-24.9), overweight (25.0-29.9), obesity (30.0-39.9) and extreme obesity (≥40.0) [81]. Blood pressure levels were measured separately up to four times and the average of these readings was used for analysis. Participants were classified as having MetS if they met at least three of the following five criteria [6, 82]:

- Increased Waist Circumference: >102 cm (males); >88 cm (females)
- High Blood Pressure: ≥130/≥85 mmHg or currently being treated for hypertension
- Elevated Triglycerides: ≥150 mg/dL
- Low HDL-Cholesterol: <40 mg/dL (males); <50 mg/dL (females)
- Elevated Fasting Glucose: ≥100 mg/dL or currently taking anti-diabetic medication

Variables anticipated a priori to be potential confounders included gender, age (years), race/ethnicity (categorized as Non-Hispanic Caucasian, Non-Hispanic African American, Mexican American or Other), socioeconomic status and education level. Age was assessed as a continuous

variable, as well as categorized by decade: 20-29, 30-39 and 40-49 years. Socioeconomic status was assessed using the Poverty Income Ratio (PIR), which is an index for the ratio of income to poverty using the Department of Health and Human Services' poverty guidelines. PIR was dichotomized as <100% and ≥100%. Education level was categorized as less than high school, high school graduate and some college or above. Smoking status was dichotomized as current smoker or non-smoker and obtained through self-report. BMI was expected to be an effect modifier and stratified estimates were obtained. However, the decision to stratify estimates also by gender was made after initial examination of the data revealed gender to be a significant effect modifier, a finding supported by the literature. CRP and fibrinogen levels were also assessed as biomarkers of systemic inflammation both as continuous and dichotomized variables. Elevated CRP was considered a value ≥1.0 mg/dL. The top quartile for fibrinogen in both genders was used as the cut-off for the dichotomized fibrinogen variable (males: >3.86 g/L; females: >4.14 g/L). Body fat percentage was obtained by performing bioelectrical impedance analysis (BIA) at mobile examination centers.

STATISTICAL ANALYSES

The fasting subsample weights were used for this analysis in order to account for the oversampling of certain participant groups (e.g., African Americans and Hispanics), as well as survey nonresponse. Weighted means or proportions with either linearized standard errors or 95% confidence intervals (95% CI) were estimated for continuous and categorical variables, respectively. Bivariate analyses between the dependent variable (MetS), the predictor of interest (CMV serostatus) and presumed confounders were performed using the means-adjusted Wald test for continuous variables and the Pearson's chi-squared test for categorical variables.

The presence of any two-way interactions between CMV and covariates was assessed by performing a stratified analysis. The Breslow-Day test for heterogeneity of odds ratios (ORs) was employed using an alpha<0.15 to determine the statistical significance of any interaction. All covariates assumed a priori to be confounders were included in a fully adjusted logistic regression model, along with any significant effect modifiers to obtain adjusted prevalence odds ratios (POR) and 95% confidence intervals (95% CI). Manual backwards selection was then employed and covariates were retained in the final model only if their absence changed the POR estimate by >10%. Model goodness-of-fit was assessed using the Archer-Lemeshow F-adjusted mean residual test, where non-significant tests indicate good fit. Poisson regression was used for assessing the association between CMV and the count of individual MetS components. A p-value <0.05 was considered statistically significant. All

statistical analyses were performed using Stata version 13 (Stata Corp LP, Texas) or SUDAAN 10.0.1 (Research Triangle Institute, Research Triangle Park, NC) with SAS 9.3 (SAS Institute, Cary, NC).

RESULTS

DESCRIPTIVE CHARACTERISTICS

Of the total 2,532 participants eligible for this analysis, approximately half were female (48.6%; SE=0.9), while the majority were Non-Hispanic Caucasian (68.2%; SE=1.9) and considered at or above the federal poverty level (85.8%; SE=1.0). Roughly a quarter of the total study population met the definition of MetS (24.9%; SE=1.1) while a little over half of the population was CMV seropositive (53.8%; SE=1.3). The seroprevalence of CMV was higher in females compared to males (61.3% vs. 46.6%, respectively; p<0.001) (**Table1**). In contrast, males had a slightly higher prevalence of MetS than females (26.9% vs. 22.8%, SE=1.2, respectively; p=0.04).

Factors significantly associated with CMV seroprevalence common to both males and females included race/ethnicity other than Non-Hispanic Caucasian, falling below the poverty line and having a lower level of education. The presence of abdominal obesity in males was associated with a lower odds of CMV seropositivity (POR: 0.73; 95% CI: 0.55-0.96; p=0.026); whereas in females abdominal obesity was associated with a higher odds of seropositivity (POR: 1.32; 95% CI: 1.10-1.71; p=0.04). There were also significant associations between older age and being a current smoker and the odds of CMV seropositivity in females, but not in males: females between 40-49 years of age had over twice the odds of being CMV+ than females in their twenties (95% CI: 1.51-2.90; p<0.001); whereas female current smokers had 1.5 times the odds of being CMV+ than non-smokers (95% CI: 1.04-2.16; p<0.05). In females, MetS was also associated with CMV seropositivity (POR: 1.50; 95% CI: 1.05-2.13; p=0.026), though this was not seen in males (**Table 1**).

STRATIFIED RESULTS

Bivariate associations between CMV seropositivity and several metabolic and immunologic factors are presented stratified by BMI (normal weight, overweight, obesity and extreme obesity) for each gender in **Table 2.** The prevalence of MetS in extreme obesity was significantly lower in CMV+ females than in CMV- females (56.2% vs. 82.6%, respectively; p=0.03), while the prevalence of MetS in normal weight females was higher CMV+ females than in CMV- females (4.9% vs. 0.9%, respectively; p=0.06), though this difference wasn't statistically significant. CMV- females with extreme obesity also had a significantly lower proportion of hypertriglyceridemia when compared to

their CMV+ counterparts (28.0% vs. 58.5%, respectively; p=0.028), as well as low HDL-C (58.8% vs. 92.2%, respectively; p=0.004) (**Table 2**).

Stratifying by BMI category had little effect on the association between CMV serostatus and the prevalence of MetS in males, which is consistent with the results of the Breslow-Day test for heterogeneity of odds ratios performed to assess for the presence of interaction between BMI and CMV in the male subgroup (p=0.718) **(Supplementary Table 1a)**. However, in females, this same test for interaction suggested that BMI was an effect modifier of the relationship between CMV and MetS (p=0.149), though borderline using an alpha<0.15 cut-off (**Supplementary Table 1b**). Assessment of interaction between BMI and CMV on the additive scale in females was carried out by obtaining CMV and BMI stratum-specific ORs for MetS and calculating measures of the Relative Excess Risk due to Interaction (RERI: 3.72, 95% CI: -17.12-24.56) and the synergy index (1.06, 95% CI: 0.75-1.51), neither of which indicated that interaction was present on the additive scale (**Supplementary Table 2**). For females, the dichotomous indicator for poverty (PIR) was also found to be a significant effect modifier of the association between CMV and MetS, therefore results were subsequently stratified by PIR.

LOGISTIC REGRESSION

Table 3 presents the results of both crude and adjusted models for the association between CMV and MetS in females, stratified by BMI and PIR. In unadjusted analyses, the odds of MetS was significantly higher in normal weight females below the poverty level who were CMV+ (POR: 222.50; 95% CI: 13.4-3708.9; p<0.001), as well as those at or above the poverty level (POR: 68.31; 95% CI: 7.34-635.92; p<0.001), when compared to their CMV- counterparts. In contrast, in females with extreme obesity, CMV seropositivity was associated with a lower odds of MetS, though this was only significant for those who were at or above the poverty level (POR: 0.21; 95% CI: 0.06-0.74; p=0.016).

Fully adjusted models included all covariates that were chosen a priori as potential confounders: age, race/ethnicity, education level and smoking status (see **Supplementary Table 3a** for results of the fully adjusted models for both males and females). The fit of the final model was better than the fully adjusted model, as determined by the Archer-Lemeshow F-adjusted means residual test (p=0.781 vs. p=0.523, respectively); however, 152 (13%) females were excluded from the final model due to missing data on smoking status. The stratified estimates from the final reduced model in Table 3 were adjusted for age, race/ethnicity and smoking status (education level was removed) and show that even after adjusting for these factors, CMV+ normal weight females still had a significantly higher odds of MetS compared to their CMV- counterparts when they were at or above the poverty level (aPOR: 43.25; 95%

CI: 4.14-452.31; p=0.002), as well as below it (aPOR: 146.10; 95% CI: 10.8-1980.3; p<0.001). In addition, the odds of MetS in extremely obese females at or above the poverty level was 84% lower in those who were CMV+ compared to CMV-, after adjusting for age, race/ethnicity and smoking status (aPOR: 0.16; 95% CI: 0.04-0.67; p=0.013).

POISSON REGRESSION

In order to determine whether CMV serostatus has a more subtle effect on the metabolic outcome of obese females, Poisson regression was employed using the count of MetS components as the outcome, rather than the binary MetS variable used with the logistic regression models. After stratifying by BMI and PIR, the odds of having a higher count of MetS components was significantly higher for CMV+ normal weight females below the poverty level (OR: 2.02; 95% CI: 1.36-2.99; p=0.001) compared to their CMV- counterparts, and this association persisted after adjusting for age, race/ethnicity, education level and smoking status (aOR: 1.74; 95% CI: 1.19-2.56; p=0.004). Similar to the results from the binary logistic regression models, the odds of having a higher count of MetS components in females with extreme obesity at or above the poverty level was 25% lower in CMV+ vs. CMV- individuals (aOR: 0.75; 95% CI: 0.62-0.91; p=0.005), after adjusting for age, race/ethnicity, education level and smoking status. However, in contrast with the binary MetS outcome used in Table 3, a significant association between the count of MetS components and CMV serostatus was seen in obese females at or above the poverty level after adjusting for all confounders: CMV+ females in this group had 0.87 times the odds of having a higher count of MetS components than CMV- females (95% CI: 0.76-0.98; p=0.027) (**Table 4**).

MARKERS OF INFLAMMATION

As biomarkers of systemic inflammation, CRP and fibrinogen levels were compared across CMV and BMI groups to see if they corresponded with the findings above of a higher odds of MetS in normal weight CMV+ females and a lower odds of MetS in extremely obese CMV+ females, when both were compared to their CMV- counterparts (**Figure 1**). Indeed, the odds of having elevated CRP was 3.46 times higher in CMV+ normal females compared to CMV- normal weight females (95% CI: 1.04-11.57; p=0.04), after adjusting for PIR, which was found to be a confounder of this association but not a significant effect modifier. Although both obese and extremely obese CMV+ females had a lower odds elevated CRP (aOR 0.66; 95% 0.34-1.28 and aOR: 0.95; 95% CI: 0.30-3.02, respectively), these associations were not statistically significant. A similar relationship was seen for elevated fibrinogen in obese and extremely obese females after adjusting for race/ethnicity, education level, smoking status and

PIR: CMV seropositivity was associated with over a 90% lower odds of having fibrinogen levels in the top quartile for obese females (aOR: 0.09; 95% CI: 0.02-0.58; p=0.012) and extremely obese females (aOR: 0.02; 95% CI: 0.00-0.30; p=0.007), when both groups were compared to their CMV- counterparts (data not shown).

DISCUSSION

Identifying factors in addition to obesity that contribute to the burden of MetS is necessary for better understanding the discrepancies seen in the prevalence and manifestation of MetS. The results of this analysis provide novel insight into the relationship between common and chronic sources of inflammation and the prevalence of metabolic abnormalities. As previously reported in the literature, obesity was significantly associated with MetS and elevated CRP levels in both males and females in this study. However, this analysis is unique for its finding that CMV infection yielded a significantly higher odds of MetS in normal weight females, yet lower odds of MetS in extremely obese females. Although the latter result only reached statistical significance in females who were at or above the poverty level, this was likely due to the small number of extremely obese females below the poverty level available for analysis (n=24).

One possible explanation for the significant magnitude of the association seen between CMV seropositivity and MetS in normal weight females is that the absence of obesity-induced inflammation provides a context for which the pro-inflammatory effects of CMV infection can become fully appreciable. In contrast, the inflammatory threshold required to trigger MetS may already be met or even exceeded in overweight and obese females, where any additional sources of inflammation have a minimal effect on influencing MetS outcomes. Although the implications of these results for normal weight females are intriguing, it's important to keep in mind that MetS in normal weight individuals represents only a minority of all MetS cases.

An unexpected finding of this analysis was that CMV seropositivity was associated with a decreased odds of MetS in females with extreme obesity. However, the clinical significance of this remains unclear, since the prevalence of MetS in this particular group of extremely obese CMV+ females was still higher than in any other BMI category. Nevertheless, CMV+ obese and extremely obese females were significantly less likely to have elevated levels of fibrinogen, triglycerides and low HDL-C, suggesting that CMV infection may have protective metabolic effects in the presence of obesity. While altered lipid metabolism has been reported in CMV infection, it is generally an in increase in lipids that is observed, rather than the decrease seen in this study's population of extremely

obese females. Obese individuals often have impaired immune responses, so, although purely speculative, it is possible that in the setting of excessive nutrient overload, CMV replication is significantly amplified, leading to substantial increases in the cellular uptake of lipids necessary for the production of viral progeny, thereby resulting in lower amounts of circulating lipids available for measurement.

STUDY LIMITATIONS

There are several limitations to this analysis, many of which are related to the observational and cross-sectional nature of the study, which precludes any assumptions to be made regarding cause and effect. First and foremost, there is no way to verify that CMV infection preceded the development of MetS in the study population. However, since primary CMV infection occurs predominantly in youth, the majority of pre-MetS infections should have been captured by restricting this analysis to adults ≥20 years of age.

Limitations related to the issue of information or misclassification bias include the uncertainty of which several covariates represent what they are assumed to represent in this analysis. For example, BMI, waist circumference and body fat percentage are not always comparable measures of adiposity. In particular, BMI has been criticized as an imperfect measure of obesity and predictor of MetS, leading many to advocate instead for the use of alternative measures, like body fat percentage, to classify obesity. However, when mean body fat percentage and waist circumference were compared between CMV groups within the normal weight and extreme obesity BMI categories, no significant differences were found, indicating that, at least for the purposes of this analysis, BMI was an adequate indicator of obesity. Furthermore, the lack of a significant difference in these measures within these BMI categories also indicates that the higher odds of MetS found in CMV+ normal weight females is not merely a result of these individuals having higher stores of total adiposity (as assessed by body fat percentage) or central adiposity (as assessed by waist circumference) when compared to their CMV- normal weight counterparts.

In addition, the binary indicator used in this study for CMV serostatus (positive vs. negative) in conjunction with CMV IgG antibody titer reveals very limited information about the length of infection or the extent of immune activation/reactivation to the virus, both of which are key for unraveling the relationship between chronic CMV infection, inflammation and MetS. Having data on CMV IgM antibody titers and CMV DNA viral loads would have been useful for assessing whether there were any differences in exposure or response to CMV infection and the effects these differences may have had on levels of inflammation and the prevalence of MetS.

CONCLUDING REMARKS

In conclusion, this study demonstrated that the relationship between chronic CMV infection and MetS in adult females depended on the presence or absence of obesity. Interestingly, CMV seropositivity was associated with a higher odds of MetS in normal weight females, but a lower odds of MetS in extremely obese females. Further investigation into the mechanisms behind CMV-induced metabolic abnormalities will help reveal why the effects of infection seen in this analysis differed between levels of obesity, as well as gender.

Table 1. Characteristics of the Study Population and CMV Seroprevalence Stratified by Gender: NHANES 1999-2004 (n=2,532)

		CMV Seroprevalence[2]			
	Overall[1]	Males		Females	
Characteristic	n (%)	% (95% CI)	POR (95% CI)	% (95% CI)	POR (95% CI)
Demographics					
Age (years)					
20-29	774 (29.1)	45.9 (40.2-51.8)	Reference	49.0 (43.1-54.9)	Reference
30-39	842 (34.9)	46.6 (40.7-52.6)	1.03 (0.73-1.46)	65.3 (60.0-70.3)	1.96 (1.40-2.76)**
40-49	916 (36.0)	47.2 (41.0-53.4)	1.1 (0.76-1.44)	66.7 (61.9-71.2)	2.09 (1.51-2.90)**
Gender					
Male	1308 (51.4)	-	-	-	-
Female	1224 (48.6)	-	-	-	-
Race/Ethnicity					
Non-Hispanic Caucasian	1147 (68.2)	34.9 (30.8-39.2)	Reference	49.8 (45.6-54.1)	Reference
Non-Hispanic African American	557 (12.3)	68.8 (61.4-75.4)	4.13 (2.81-6.06)**	83.3 (77.1-88.0)	5.01 (3.29-7.61)**
Mexican American	620 (9.0)	81.7 (77.0-85.6)	8.33 (5.87-11.83)**	87.1 (83.5-90.1)	6.81 (4.73-9.81)**
Other	208 (10.4)	66.3 (55.9-75.3)	3.67 (2.34-5.75)**	88.8 (80.2-93.9)	7.95 (3.90-16.21)**
Poverty Income Ratio (PIR)					
≥100%	1921 (80.5)	43.6 (40.2-47.1)	Reference	58.0 (54.2-61.6)	Reference
<100%	432 (13.3)	64.8 (58.4-70.8)	2.38 (1.85-3.07)**	77.8 (69.0-84.6)	2.53 (1.53-4.18)**
Missing	179 (6.2)	55.1 (41.6-68.0)	1.59 (0.90-2.79)	61.9 (52.4-70.5)	1.18 (0.78-1.77)
Education Level					
Less than high school	657 (17.6)	70.5 (65.5-75.0)	Reference	81.3 (75.2-86.2)	Reference
High school graduate	615 (26.3)	48.4 (42.2-54.7)	0.39 (0.29-0.54)**	67.0 (60.5-73.0)	0.47 (0.31-0.71)**
Some college or above	1255 (55.9)	37.3 (33.5-41.3)	0.25 (0.19-0.33)**	53.2 (49.3-57.1)	0.26 (0.17-0.39)**
Missing	5 (0.2)	-	-	-	-
Current Smoker					
No	1423 (54.1)	46.2 (41.4-51.0)	Reference	57.9 (54.5-61.3)	Reference
Yes	711 (28.7)	48.0 (42.9-53.2)	1.08 (0.79-1.47)	67.3 (59.6-74.3)	1.50 (1.04-2.16)*
Missing	398 (17.2)	45.4 (37.8-53.3)	0.97 (0.69-1.37)	64.2 (55.6-71.9)	1.30 (0.90-1.89)
BMI (kg/m^2)					
Normal Weight (18.5-24.9)	873 (37.2)	48.8 (43.3-54.4)	Reference	55.6 (50.8-60.2)	Reference
Overweight (25.0-29.9)	877 (33.6)	48.5 (43.1-54.0)	0.99 (0.72-1.35)	62.5 (57.1-67.8)	1.33 (0.99-1.81)
Obesity (30.0-39.9)	642 (24.3)	42.1 (34.9-50.0)	0.76 (0.53-1.09)	68.2 (62.2-73.7)	1.72 (1.25-2.35)**
Extreme Obesity (≥40)	140 (4.9)	34.5 (18.4-55.1)	0.55 (0.22-1.36)	67.1 (55.0-77.3)	1.63 (0.96-2.77)
Metabolic & Immunological Characteristics					
Metabolic Syndrome					
No MetS	1897 (75.1)	46.7 (43.1-50.4)	Reference	59.2 (55.8-62.5)	Reference
MetS	635 (24.9)	46.3 (40.0-53.2)	0.98 (0.73-1.33)	68.5 (61.3-75.0)	1.50 (1.05-2.13)*
Number of MetS Components					
0-1	1363 (54.6)	47.2 (42.5-52.0)	Reference	58.5 (54.7-62.2)	Reference
2-3	919 (35.3)	46.1 (40.2-52.2)	0.96 (0.70-1.31)	64.7 (59.5-69.6)	1.30 (1.02-1.67)*
4-5	250 (10.0)	45.2 (36.5-54.3)	0.92 (0.63-1.36)	65.8 (53.5-76.3)	1.37 (0.78-2.39)
Presence of Individual Components					
Abdominal Obesity	1089 (41.6)	41.3 (35.8-47.1)	0.73 (0.55-0.96)*	64.5 (60.0-68.7)	1.32 (1.01-1.71)*
High BP	618 (24.2)	48.0 (41.9-54.1)	1.08 (0.83-1.41)	69.0 (60.0-76.7)	1.50 (0.96-2.35)
Hypertriglyceridemia	710 (27.9)	44.1 (49.1-49.3)	0.86 (0.68-1.08)	62.6 (55.1-69.5)	1.07 (0.74-1.54)
Low HDL-C	940 (36.7)	49.8 (43.8-55.8)	1.21 (0.92-1.59)	66.0 (61.1-70.6)	1.40 (1.09-1.81)*
High Fasting Glucose	642 (24.4)	48.4 (42.7-54.2)	1.11 (0.80-1.54)	66.6 (59.0-73.4)	1.32 (0.91-1.90)
C-Reactive Protein (CRP)					
Not Elevated (<1.0 mg/dL)	2315 (91.6)	46.3 (42.7-49.9)	Reference	60.5 (57.1-63.7)	Reference
Elevated (≥1.0 mg/dL)	217 (8.4)	52.7 (38.1-67.0)	1.29 (0.68-2.45)	67.8 (58.9-75.6)	1.38 (0.90-2.10)
Fibrinogen[3]					
Not Elevated	479 (19.0)	46.9 (39.3-54.7)	Reference	71.0 (64.6-76.7)	Reference
Elevated	151 (4.8)	55.5 (37.4-72.2)	1.41 (0.67-2.94)	59.5 (43.4-73.8)	0.60 (0.29-1.25)
Missing	1902 (76.2)	45.9 (42.2-49.7)	0.96 (0.69-1.33)	58.9 (55.3-62.5)	0.59 (0.41-0.83)
CMV Seropositive	1591 (53.8)	46.6 (43.3-50.0)	-	61.3 (58.3-64.3)	-

POR: prevalence odds ratio; MetS: metabolic syndrome

[1]Number of participants, n, and weighted prevalence (%) of characteristics listed for entire study population

[2]Weighted seroprevalence % (95% confidence intervals) of CMV by characteristic listed, as well as POR (95% CI)

[3]Top quartile of fibrinogen (g/L) for each gender was used as cut-off for defining elevatated fibrinogen

*p<0.05; **p<0.01

Table 2. Bivariate Associations Between CMV and Metabolic Factors Stratified by BMI and Gender (n=2,532)[1,2]

	Normal Weight (n=438)			**Overweight** (n=523)			**Obesity** (n=302)			**Extreme Obesity** (n=45)		
Males	CMV-	CMV+	p-value	CMV-	CMV+	p-value	CMV-	CMV+	p-value	CMV-	CMV+	p-value
MetS (%)	3.3 (1.5)	4.9 (1.8)	0.478	20.9 (3.0)	24.0 (2.8)	0.481	59.3 (5.0)	60.5 (4.7)	0.861	65.0 (10.5)	83.4 (6.3)	0.135
Mean # of MetS Components	0.7 (0.1)	0.8 (0.1)	0.213	1.5 (0.1)	1.6 (0.1)	0.410	2.7 (0.1)	2.7 (0.1)	0.582	3.0 (0.3)	3.4 (0.2)	0.298
Number of MetS Components (%)			0.489			0.390			0.739			0.463
0-1	85.8 (3.2)	80.7 (3.1)		51.5 (3.1)	51.7 (4.0)		19.5 (3.9)	20.8 (3.3)		15.6 (7.6)	4.7 (3.6)	
2-3	13.6 (3.1)	17.6 (3.2)		43.1 (2.8)	39.6 (4.1)		53.3 (4.0)	56.0 (5.5)		40.1 (8.0)	40.2 (13.3)	
4-5	0.6 (0.6)	1.6 (1.1)		5.4 (1.6)	8.6 (1.9)		27.1 (3.8)	23.1 (4.2)		44.2 (10.0)	55.1 (13.4)	
Individual MetS Components (%)												
Abdominal Obesity	1.0 (1.0)	1.1 (1.0)	0.950	22.7 (2.9)	16.3 (2.8)	0.080	87.3 (3.3)	89.7 (2.6)	0.533	100.00	100.0	-
High BP	12.9 (3.1)	19.9 (2.6)	0.106	28.8 (3.1)	32.1 (3.6)	0.487	48.4 (4.7)	44.4 (4.9)	0.543	45.5 (11.8)	56.7 (11.5)	0.496
Hypertriglyceridemia	15.7 (2.6)	17.8 (2.6)	0.554	40.6 (3.3)	35.8 (3.3)	0.284	51.6 (4.2)	45.6 (5.3)	0.400	49.6 (8.8)	65.0 (9.9)	0.226
Low HDL-C	16.9 (3.6)	21.2 (3.8)	0.400	30.6 (3.3)	34.7 (3.4)	0.364	43.7 (4.1)	53.4 (4.8)	0.099	48.6 (10.0)	54.1 (14.4)	0.744
High Fasting Glucose	19.7 (3.5)	20.1 (3.1)	0.928	27.8 (3.1)	41.2 (3.7)	0.015	42.6 (4.9)	32.3 (4.8)	0.163	58.8 (9.8)	62.0 (10.4)	0.812
Waist Circumference (cm)	84.8 (0.6)	82.7 (0.6)	0.023	97.5 (0.4)	96.2 (0.4)	0.020	113.1 (0.9)	111.5 (1.0)	0.227	142.9 (2.6)	134.9 (2.3)	0.061
Mean Body Fat Percentage	21.4 (0.6)	20.9 (0.6)	0.584	24.3 (0.6)	24.6 (0.4)	0.695	29.6 (0.7)	29.0 (0.8)	0.557	32.6 (2.7)	33.3 (2.5)	0.858
CRP (mg/dL)	0.16 (0.02)	0.23 (0.04)	0.163	0.33 (0.08)	0.30 (0.05)	0.719	0.69 (0.15)	0.73 (0.15)	0.866	0.34 (0.03)	0.54 (0.12)	0.080
Elevated CRP (%)	2.2 (1.1)	3.5 (1.3)	0.520	3.8 (1.8)	4.6 (1.5)	0.719	4.7 (2.0)	7.0 (2.1)	0.417	19.2 (8.9)	30.2 (13.4)	0.495
Fibrinogen (g/L)	3.0 (0.1)	3.4 (0.1)	0.028	3.1 (0.1)	3.3 (0.1)	0.219	3.5 (0.1)	3.6 (0.1)	0.419	4.4 (0.1)	4.0 (0.2)	0.147
Elevated Fibrinogen (%)	6.4 (4.6)	23.8 (6.6)	0.110	10.1 (5.1)	25.5 (6.0)	0.080	23.0 (7.2)	24.4 (6.5)	0.882	100.00	28.0 (19.1)	0.001
CMV IgG Optical Density	-	1.9 (0.1)	-	-	2.0 (0.0)	-	-	1.9 (0.1)	-	-	2.1 (0.2)	-
	Normal Weight (n=435)			**Overweight** (n=354)			**Obesity** (n=340)			**Extreme Obesity** (n=95)		
Females	CMV-	CMV+	p-value	CMV-	CMV+	p-value	CMV-	CMV+	p-value	CMV-	CMV+	p-value
MetS (%)	0.9 (0.9)	4.9 (1.4)	0.064	22.8 (6.2)	26.1 (3.7)	0.653	38.1 (4.8)	45.3 (3.5)	0.307	82.6 (7.3)	56.2 (5.2)	0.030
Mean # of MetS Components	0.4 (0.1)	0.6 (0.1)	0.062	1.7 (0.2)	1.7 (0.1)	0.778	2.5 (0.1)	2.4 (0.1)	0.835	3.2 (0.2)	2.8 (0.1)	0.126
Number of MetS components (%)			0.360			0.401			0.007			0.519
0-1	94.2 (2.5)	89.7 (2.0)		48.5 (6.2)	43.1 (4.7)		10.6 (2.9)	25.4 (3.1)		2.5 (2.5)	9.0 (4.0)	
2-3	4.9 (2.3)	9.3 (2.0)		43.2 (5.7)	51.7 (4.3)		72.0 (5.3)	53.1 (4.1)		61.0 (11.5)	61.4 (6.8)	
4-5	0.9 (0.9)	1.0 (0.6)		8.2 (3.3)	5.2 (1.4)		17.5 (4.3)	21.4 (2.8)		36.5 (11.5)	29.6 (6.7)	
Individual MetS Components (%)												
Abdominal Obesity	4.6 (1.9)	8.9 (2.0)	0.202	73.6 (4.8)	59.4 (5.3)	0.054	100.00	98.8 (0.8)	-	100.00	100.0	-
High BP	5.7 (1.9)	10.7 (2.4)	0.114	14.1 (3.9)	13.7 (2.8)	0.930	26.6 (5.4)	32.2 (3.9)	0.446	45.2 (11.3)	47.0 (6.6)	0.893
Hypertriglyceridemia	9.3 (3.6)	7.7 (1.9)	0.685	23.2 (5.1)	27.9 (2.9)	0.464	33.4 (5.1)	32.8 (3.2)	0.923	58.5 (1.0)	28.0 (7.2)	0.028
Low HDL-C	18.6 (3.8)	27.3 (2.8)	0.133	37.7 (4.8)	54.9 (4.5)	0.012	61.3 (6.6)	53.8 (3.6)	0.348	92.2 (4.6)	58.8 (7.0)	0.004
High Fasting Glucose	5.9 (2.0)	8.2 (2.0)	0.423	19.0 (5.4)	16.8 (2.7)	0.685	26.3 (5.4)	26.7 (2.8)	0.945	28.5 (14.2)	48.2 (7.5)	0.258
Waist Circumference (cm)	77.6 (0.6)	79.1 (0.5)	0.072	91.3 (0.6)	90.3 (0.5)	0.264	105.0 (1.1)	105.0 (0.7)	0.993	128.1 (2.3)	124.2 (1.2)	0.178
Mean Body Fat Percentage	35.5 (0.5)	35.3 (0.4)	0.776	40.1 (0.6)	40.2 (0.4)	0.836	45.0 (0.6)	43.3 (0.5)	0.026	46.4 (0.8)	47.9 (0.8)	0.215
CRP (mg/dL)	0.22 (0.03)	0.25 (0.02)	0.380	0.37 (0.03)	0.42 (0.05)	0.419	0.67 (0.07)	0.66 (0.08)	0.901	1.75 (0.59)	1.18 (0.16)	0.258
Elevated CRP (%)	2.6 (1.2)	6.0 (1.5)	0.111	6.3 (2.5)	10.9 (3.6)	0.300	24.0 (4.5)	18.4 (3.5)	0.311	42.0 (12.0)	44.0 (5.4)	0.880
Fibrinogen (g/L)	3.3 (0.1)	3.2 (0.1)	0.474	3.5 (0.1)	3.7 (0.2)	0.395	4.0 (0.3)	3.8 (0.1)	0.292	5.2 (0.8)	4.5 (0.2)	0.288
Elevated Fibrinogen (%)	13.5 (7.7)	6.1 (3.0)	0.290	13.1 (7.5)	19.0 (5.9)	0.586	36.6 (11.6)	16.0 (3.6)	0.069	72.0 (17.6)	67.7 (12.1)	0.806
CMV IgG Optical Density	-	2.2 (0.0)	-	-	2.3 (0.1)	-	-	2.3 (0.0)	-	-	2.3 (0.1)	-

[1]Data presented as weighted percentage or mean (linearized standard error).

[2]P-values calculated with Pearson's chi-squared test or means adjusted Wald test.

Table 3. Unadjusted and Adjusted Prevalence Odds Ratios for Association between CMV and Metabolic Syndrome in Females Stratified by BMI and Poverty Level (Logistic Regression)

	Sample	**Normal Weight**				**Overweight**				**Obesity**				**Extreme Obesity**					
Outcome=MetS	Size	n*	POR	95% CI	p-value	n*	POR	95% CI	p-value	n*	POR	95% CI	p-value	n*	POR	95% CI	p-value	*F-stat*[2]	*p-value*
CMV (Crude)	1126																	*1.88*	*0.093*
PIR≥100%		10/330	68.31	(7.34-635.92)	<0.001	62/257	0.94	(0.39-2.23)	0.878	94/247	1.04	(0.57-1.88)	0.892	36/62	0.21	(0.06-0.74)	0.016		
PIR<100%		4/63	222.50	(13.4-3708.9)	<0.001	21/70	3.05	(0.73-12.77)	0.124	35/71	3.39	(0.68-16.96)	0.134	15/26	0.67	(0.11-3.95)	0.654		
CMV (Final Model[1])	974																	*0.61*	*0.781*
PIR≥100%		8/277	43.25	(4.14-452.31)	0.002	53/215	0.73	(0.25-2.08)	0.547	85/214	0.86	(0.41-1.81)	0.681	32/55	0.16	(0.04-0.67)	0.013		
PIR<100%		4/59	146.10	(10.8-1980.3)	<0.001	19/63	2.46	(0.55-10.99)	0.232	34/67	2.90	(0.58-14.44)	0.188	13/24	0.54	(0.09-3.35)	0.500		

POR: prevalence odds ratio; PIR: poverty-to-income ratio (≥100%: at or above federal poverty level; <100%: below federal poverty level)

*Number of events over stratum-specific sample size

[1]Final Model adjusted for: age, race/ethnicity and smoking (education dropped)

[2]Model goodness-of-fit assessed using the Archer-Lemeshow F-adjusted mean residual test

Table 4. Unadjusted and Adjusted Odds Ratios for Association between CMV and Count of Metabolic Syndrome Components in Females Stratified by BMI and Poverty Level (Poisson Regression)

Outcome=No. of MetS Components	Sample Size	**Normal Weight**				**Overweight**				**Obesity**				**Extreme Obesity**			
		n*	OR	95% CI	p-value	n*	OR	95% CI	p-value	n*	OR	95% CI	p-value	n*	OR	95% CI	p-value
CMV (Crude)	1126																
PIR≥100%		330	1.41	(0.98-2.02)	0.060	257	0.95	(0.75-1.20)	0.663	247	0.92	(0.82-1.02)	0.111	62	0.78	(0.65-0.94)	0.009
PIR<100%		63	2.02	(1.36-2.99)	0.001	70	1.36	(0.97-1.90)	0.070	71	1.31	(0.94-1.82)	0.104	26	1.12	(0.79-1.57)	0.519
CMV (Final Model[1])	973																
PIR≥100%		277	1.25	(0.87-1.80)	0.221	215	0.85	(0.65-1.10)	0.210	213	0.87	(0.76-0.98)	0.027	55	0.75	(0.62-0.91)	0.005
PIR<100%		59	1.74	(1.19-2.56)	0.005	63	1.18	(0.86-1.62)	0.290	67	1.21	(0.89-1.63)	0.212	24	1.05	(0.77-1.43)	0.760

PIR: poverty-to-income ratio (≥100%: at or above federal poverty level; <100%: below federal poverty level)

*Stratum-specific sample size

[1]Final Model fully adjusted for: age, race/ethnicity, education and smoking

Supplementary Table 1a. Assessing for Interaction and Confounding of the Association between CMV and MetS in MALES

Adjusted for:	OR	95% CI	p-value	Heterog. p-value[1]
Nothing (Crude)	0.98	(0.73-1.33)	0.914	-
Age (continuous)	0.98	(0.73-1.31)	0.863	0.902
Race/Ethnicity	1.14	(0.79-1.63)	0.477	0.848
PIR	1.05	(0.77-1.42)	0.765	0.494
Education Level	0.95	(0.69-1.30)	0.730	0.702
Current Smoker	1.00	(0.71-1.42)	0.990	0.513
BMI categorical	1.19	(0.83-1.73)	0.329	0.718
BMI (kg/m2)	1.25	(0.87-1.78)	0.224	0.330

[1]calculated with the Breslow-Day test for heterogeneity of odds ratios

Supplementary Table 1b. Assessing for Interaction and Confounding of the Association between CMV and MetS in FEMALES

Adjusted for:	OR	95% CI	p-value	Heterog. p-value[1]
Nothing (Crude)	1.50	(1.05-2.13)	0.026	-
Age (continuous)	1.36	(0.93-2.00)	0.113	0.171
Race/Ethnicity	1.36	(0.95-1.95)	0.093	0.883
PIR	1.34	(0.93-1.93)	0.113	0.052
Education Level	1.34	(0.93-1.93)	0.111	0.981
Current Smoker	1.36	(0.94-1.95)	0.099	0.803
BMI categorical	1.23	(0.82-1.85)	0.315	0.149
BMI (kg/m2)	1.27	(0.86-1.88)	0.223	0.068

[1]calculated with the Breslow-Day test for heterogeneity of odds ratios

Supplementary Table 2. Analysis of Interaction Between CMV and BMI on the Odds of Metabolic Syndrome

	Normal Weight			**Overweight/Obesity**			*CMV Stratum-Specific*		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Females									
CMV-	1.00	Reference	-	56.54	(7.6-419.4)	<0.001	*56.54*	*(7.6-419.4)*	*<0.001*
CMV+	5.35	(0.7-38.7)	0.095	64.61	(9.4-442.5)	<0.001	*12.07*	*(6.3-23.1)*	*<0.001*
BMI Stratum-Specific	*5.35*	*(0.7-38.7)*	*0.095*	*1.14*	*(0.8-1.7)*	*0.489*			
Measures of Interaction on Additive Scale									
RERI[1]: 3.72 (-17.12-24.56)									
AP[2]: 0.06 (-0.27-0.38)									
Synergy Index: 1.06 (0.75-1.51)									
Measure of Interaction on Multiplicative Scale									
CMV*BMI OR: 0.21 (0.03-1.62)									
Males									
CMV-	1.00	Reference	-	18.06	(7.4-43.9)	<0.001	*18.06*	*(7.4-43.9)*	*<0.001*
CMV+	1.53	(0.5-5.1)	0.481	18.20	(6.7-49.5)	<0.001	*11.90*	*(5.4-26.1)*	*<0.001*
BMI Stratum-Specific	*1.53*	*(0.5-5.1)*	*0.481*	*1.01*	*(0.8-1.3)*	*0.955*			
Measures of Interaction on Additive Scale									
RERI[1]: -0.38 (-5.17-4.40)									
AP[2]: -0.02 (-0.29-0.25)									
Synergy Index: 0.98 (0.74-1.29)									
Measure of Interaction on Multiplicative Scale									
CMV*BMI OR: 0.66 (0.21-2.07)									

[1]Relative excess risk due to interaction

[2]Proportion attributable to the interaction

Supplementary Table 3a. Unadjusted and Adjusted Prevalence Odds Ratios for Association between CMV and Metabolic Syndrome in **Females** Stratified by BMI and Poverty Level (Logistic Regression)

	Sample	Normal Weight				Overweight				Obesity				Extreme Obesity					
Outcome=MetS	Size	n*	POR	95% CI	p-value	n*	POR	95% CI	p-value	n*	POR	95% CI	p-value	n*	POR	95% CI	p-value	*F-stat*[3]	*p-value*
CMV (Crude)	1126																	*1.88*	*0.093*
PIR≥100%		10/330	68.31	(7.4-635.92)	<0.001	62/257	0.94	(0.39-2.23)	0.878	94/247	1.04	(0.57-1.88)	0.892	36/62	0.21	(0.06-0.74)	0.016		
PIR<100%		4/63	222.50	(13.4-3708.9)	<0.001	21/70	3.05	(0.73-12.77)	0.124	35/71	3.39	(0.68-16.96)	0.134	15/26	0.67	(0.11-3.95)	0.654		
CMV (Fully Adjusted[1])	973																	*0.92*	*0.523*
PIR≥100%		8/277	40.76	(3.82-434.98)	0.003	53/215	0.67	(0.23-1.93)	0.445	85/213	0.82	(0.38-1.77)	0.605	32/55	0.16	(0.04-0.64)	0.011		
PIR<100%		4/59	150.59	(11.0-2059.6)	<0.001	19/63	2.46	(0.53-11.35)	0.241	34/67	3.03	(0.58-15.85)	0.185	13/24	0.58	(0.09-3.59)	0.549		
CMV (Final Model[2])	974																	*0.61*	*0.781*
PIR≥100%		8/277	43.25	(4.14-452.31)	0.002	53/215	0.73	(0.25-2.08)	0.547	85/214	0.86	(0.41-1.81)	0.681	32/55	0.16	(0.04-0.67)	0.013		
PIR<100%		4/59	146.10	(10.8-1980.3)	<0.001	19/63	2.46	(0.55-10.99)	0.232	34/67	2.90	(0.58-14.44)	0.188	13/24	0.54	(0.09-3.35)	0.500		

POR: prevalence odds ratio; PIR: poverty-to-income ratio (≥100%: at or above federal poverty level; <100% below federal poverty level)

*Number of events over stratum-specific sample size

[1]Fully adjusted for: age, race/ethnicity, education and smoking

[2]Final Model adjusted for: age, race/ethnicity and smoking

[3]Model goodness-of-fit assessed using the Archer-Lemeshow F-adjusted mean residual test

Supplementary Table 3b. Unadjusted and Adjusted Prevalence Odds Ratios for Association between CMV and Metabolic Syndrome in **Males** Stratified by BMI and Poverty Level (Logistic Regression)

	Sample	Normal Weight				Overweight				Obesity				Extreme Obesity					
Outcome=MetS	Size	n*	POR	95% CI	p-value	n*	POR	95% CI	p-value	n*	POR	95% CI	p-value	n*	POR	95% CI	p-value	*F-stat*[3]	*p-value*
CMV (Crude)	1308	15/438	1.53	(0.46-5.11)	0.481	115/523	1.19	(0.72-1.97)	0.481	172/302	1.05	(0.59-1.87)	0.861	29/45	2.70	(0.72-10.21)	0.139	*4.54*	*0.001*
CMV (Fully Adjusted[1])	1011	11/356	1.70	(0.41-7.11)	0.457	80/395	1.33	(0.76-2.33)	0.314	128/225	1.49	(0.68-3.28)	0.314	23/35	4.16	(0.95-18.14)	0.058	*12.28*	*<0.001*
CMV (Final Model[2])	1305	15/437	1.61	(0.44-5.88)	0.460	114/521	1.27	(0.77-2.10)	0.334	172/302	1.28	(0.67-2.45)	0.452	29/45	3.89	(0.98-15.42)	0.053	*1.75*	*0.114*

POR: prevalence odds ratio

*Number of events over stratum-specific sample size

[1]Fully adjusted for: age, race/ethnicity, education, smoking and PIR (poverty-to-income ratio)

[2]Final Model adjusted for: age, race/ethnicity and education

[3]Model goodness-of-fit assessed using the Archer-Lemeshow F-adjusted mean residual test

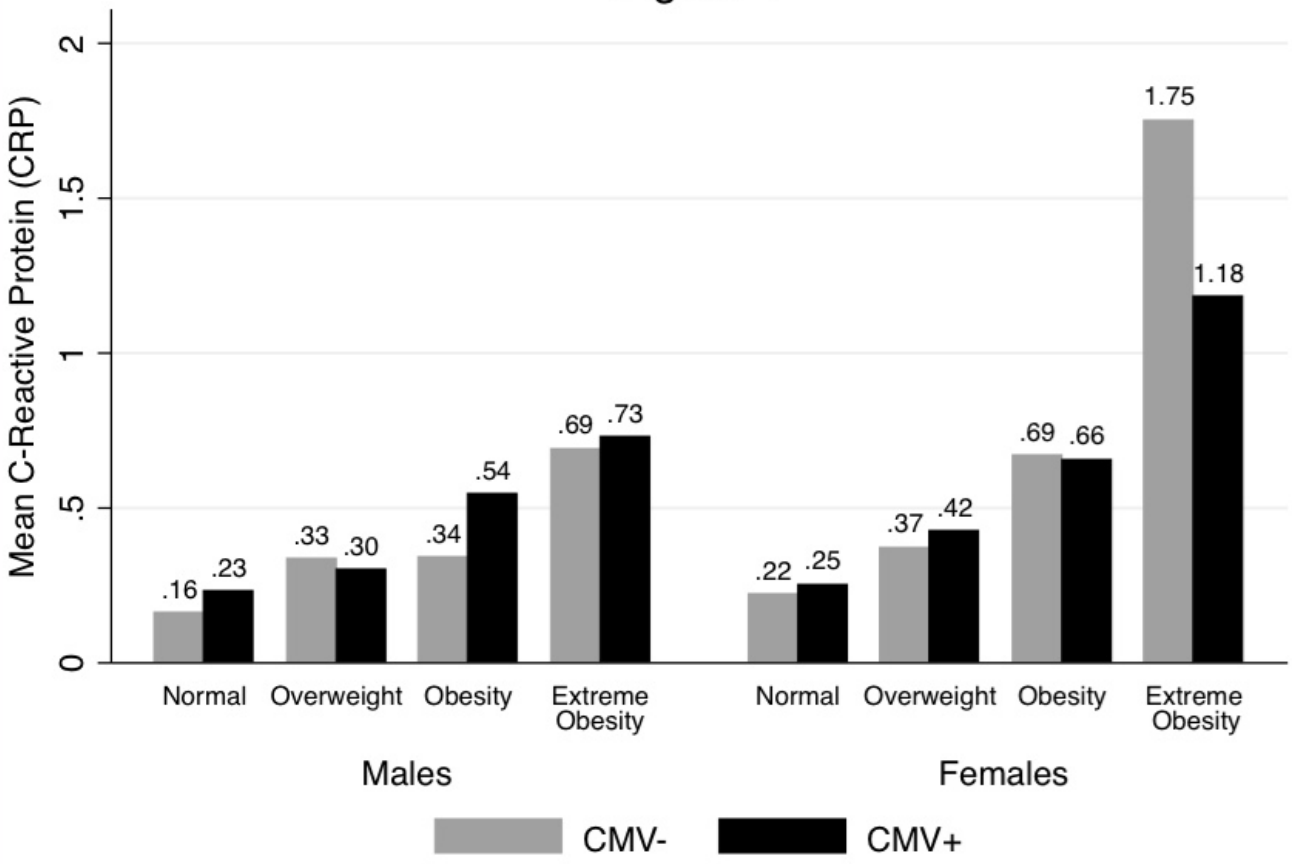
Supplementary Table 4. Proportion of Individual MetS Components in Females Stratified by BMI

	Normal Weight				Overweight				Obesity				Extreme Obesity			
MetS Components	**All (n=435)**	CMV- (n=166)	CMV+ (n=269)	p-value	**All (n=354)**	CMV- (n=103)	CMV+ (n=251)	p-value	**All (n=340)**	CMV- (n=84)	CMV+ (n=256)	p-value	**All (n=95)**	CMV- (n=22)	CMV+ (n=73)	p-value
Abdominal Obesity	**7.0 (1.3)**	4.6 (1.9)	8.9 (2.0)	0.202	**64.7 (3.8)**	73.6 (4.8)	59.4 (5.3)	0.054	**99.2 (0.5)**	100.00	98.8 (0.8)	0.295	**100.00**	100.00	100.00	N/A
High BP	**8.5 (1.6)**	5.7 (1.9)	10.7 (2.4)	0.114	**13.8 (2.2)**	14.1 (3.9)	13.7 (2.8)	0.930	**30.4 (3.0)**	26.6 (5.4)	32.2 (3.9)	0.446	**46.4 (5.9)**	45.2 (11.3)	47.0 (6.6)	0.893
Hypertriglyceridemia	**8.4 (1.9)**	9.3 (3.6)	7.7 (1.9)	0.685	**26.1 (2.5)**	23.2 (5.1)	27.9 (2.9)	0.464	**33.0 (2.8)**	33.4 (5.1)	32.8 (3.2)	0.923	**38.0 (5.5)**	58.5 (10.0)	28.0 (7.2)	0.028
Low HDL-C	**23.4 (2.0)**	18.6 (3.8)	27.3 (2.8)	0.133	**48.5 (3.4)**	37.7 (4.8)	54.9 (4.5)	0.012	**56.2 (3.1)**	61.3 (6.6)	53.8 (3.6)	0.348	**69.8 (5.3)**	92.2 (4.6)	58.8 (7.0)	0.004
High Fasting Glucose	**7.2 (1.5)**	5.9 (2.0)	8.2 (2.0)	0.423	**17.6 (2.9)**	19.0 (5.4)	16.8 (2.7)	0.685	**26.6 (2.4)**	26.3 (5.4)	26.7 (2.8)	0.945	**41.7 (7.1)**	28.5 (14.2)	48.2 (7.5)	0.258

[1]Data presented as weighted percentage (linearized standard error).

[2]P-values calculated with Pearson's chi-squared tes

Figure 1


Mean C-Reactive Protein (CRP)
0
.5
1
1.5
2
.16
.23
.33
.30
.34
.54
.69
.73
.22
.25
.37
.42
.69
.66
1.75
1.18
Normal
Overweight
Obesity
Extreme Obesity
Normal
Overweight
Obesity
Extreme Obesity
Males
Females
CMV-
CMV+

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